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NEW PROCESS

Field of the Invention

The present invention relates to a new process for the preparation and resolution of mandelic acid derivatives from racemic mandelic acid derivative mixtures by salt formation with chiral base cyclic amides. The invention also relates to mandelic acid derivative cyclic amide salts as well as to the use of the resolved mandelic acid derivatives as intermediates suitable for large-scale manufacturing of, for example, pharmaceutical compounds.

Prior Art

Various amines have been reported as resolving agents for mandelic acid derivatives. For the resolution of mandelic acids a number of chiral amines has been described, *e.g.* α-methylbenzylamine, 2-benzylamino-1-butanol, (*R*)-2-*tert*-butyl-3-methylimidazolidin-4-one (BMI), (+)-cinchonine, brucine, quinine, quinidine, (-)-ephedrine, (-)-2-amino-1-butanol, amphetamine and adrenaline. These amines as well as others are described in E.J. Ebbers et al. *Tetrahedron: Asymmetry* **1997**, *8*, 4047-4057 and references cited therein.

In J. Hoover et al., (*J. Med. Chem.* **1974**, *17*, 34-41) are disclosed 21 substituted mandelic acids with references to original literature. The described resolving bases are (-)-ephedrine, brucine, and (+)-α-methylbenzylamine.

J. Nieuwenhuijzen et al. (*Angew. Chem. Int. Ed.* **2002**, *41*, 4281-4286) describes the resolution of 4-chloromandelic acid with α-methylbenzylamine with or without a 1:1 *ortho:para* mixture of nitro-substituted α-methylbenzylamine (10mol%).

JP2001072644 describes optical resolution of 2-chloromandelic acid with *N*-benzyl-α-methylbenzylamine and derivatives thereof.

JP 1221345 describes optical resolution of phenyl-substituted mandelic acid derivatives with amino acid hydrazines.

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However, there remains a need for further means for resolving mandelic acid derivatives. Mandelic acids are used in the manufacture of a range of interesting molecules, such as pharmaceuticals. Thus, the invention also relates to the use of the resolved mandelic acid derivatives as intermediates suitable for large-scale manufacturing of, for example pharmaceutical compounds, e.g. compounds as described in WO 02/44145.

A number of bases, including such decribed in the art, were tested in order to obtain good resolution of mandelic acid derivatives (especially 3-chloro-5-difluoromethoxymandelic acid), e.g. α-methylbenzylamine, (*S*)-1-naphthylethylamine, (+)-cinchonine, (+)-dihydroabietylamine, (*S*)-2-amino-2-phenylethanol, (-)-ephedrine, L-phenylalaniole, and α,α-diphenyl-D-prolinole. None of these yielded particularly satisfactory results for large-scale manufacturing purposes. We have now surprisingly found that racemic mandelic acid derivatives may be resolved by salt formation with chiral base cyclic amides, such as proline amide.

Description of the Invention

According to a first aspect of the invention, there is provided a process for resolving (*R*)- or (*S*)- optionally substituted mandelic acids from racemic mixturers of said optionally substituted mandelic acids by salt formation with a chiral base (D)- or (L)-cyclic amide, comprising the steps:

(a) forming a mixture in ethyl acetate/water of a racemic optionally substituted mandelic acid; and a chiral base (D)- or (L)-cyclic amide, wherein the base used is (D) for separation of (*R*) acids, and (L) for separation of (*S*) acids, at an acid : base molar ratio of 1 : 0.48-0.52; and wherein the water is in the range of 5 to 15 % (vol.) of ethyl acetate; then

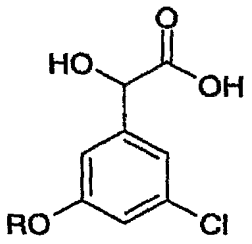
(b) heating and stirring said mixture at reflux; then

(c) cooling said mixture/suspension from step (b), followed by filtering said cooled mixture/suspension to obtain the respective *R*/D or *S*/L mandelic acid cyclic amide salt.

It is to be understood that said "(*R*)- or (*S*)-optionally substituted mandelic acids" may be as described in WO 02/44145, and wherein said definitions and disclosed optionally substituted mandelic acids are incorporated into this specification by reference.

According to another aspect of the invention there is provided a process for resolving (*R*)- or (*S*)-mandelic acid derivatives from racemic mandelic acid derivatives by salt formation with a chiral base (D)- or (L)-cyclic amide, comprising the steps:

(a) forming a mixture in ethyl acetate/water of a racemic mandelic acid derivative of formula **I**;

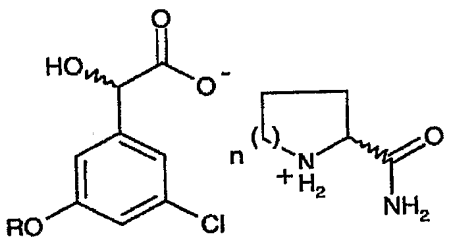


I

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and a chiral base (D)- or (L)-cyclic amide wherein the base used is (D) for separation of (*R*) acids, and (L) for separation of (*S*) acids, at an acid : base molar ratio of 1 : 0.48-0.52; and wherein the water is in the range of 5 to 15 % (vol.) of ethyl acetate; then

(b) heating and stirring said mixture at reflux; then

(c) cooling said mixture/suspension from step (b), followed by filtering said cooled mixture/suspension to obtain the respective (*R*)/(D) or (*S*)/(L) mandelic acid cyclic amide salt of formula **II**;



II

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and n is 0, 1 or 2.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-6}' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

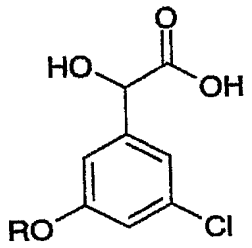
In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but is not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl, t-hexyl.

In this specification, unless otherwise stated, the term "cyclic amide" includes but is not limited to, proline amide, azetidine-2-carboxamide and piperidine-2-carboxamide as well as substituted forms thereof.

In this specification, unless otherwise stated, the term "ethyl acetate" means ethyl acetate, which, however, may be substituted by another acetate, such as propyl acetate or butyl acetate.

In another aspect of the invention, there is provided a process for resolving (*R*)-mandelic acid derivatives from racemic mandelic acid derivatives by salt formation with a chiral base (D)-cyclic amide, comprising the steps:

(a) forming a mixture in ethyl acetate/water of a racemic mandelic acid derivative of formula I;

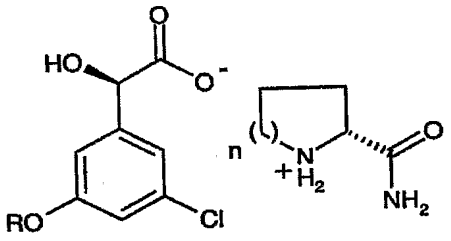


I

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and a chiral base (D)-cyclic amide, at an acid : base molar ratio of 1 : 0.48-0.52; and wherein the water is in the range of 5 to 15 % (vol.) of ethyl acetate; then

(b) heating and stirring said mixture at reflux; then

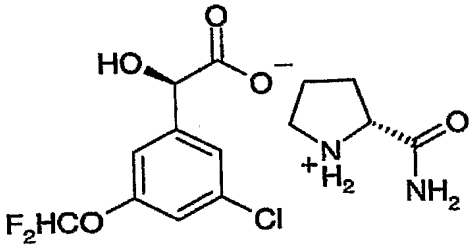
(c) cooling said mixture/suspension from step (b), followed by filtering said cooled mixture/suspension to obtain a mandelic acid cyclic amide salt of formula **III**;



III

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and n is 0, 1 or 2.

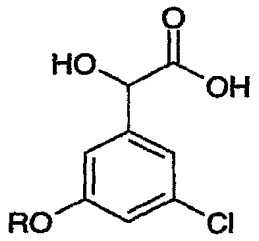
In one embodiment of this aspect there is provided a process wherein R of Formula **III** is CHF_2, and n of Formula **III** is 1, represented by Formula **VI**;



VI

In another aspect of the invention, there is provided a process for resolving (*S*)-mandelic acid derivatives from racemic mandelic acid derivatives by salt formation with a chiral base (L)-cyclic amide, comprising the steps:

(a) forming a mixture in ethyl acetate/water of a racemic mandelic acid derivative of formula **I**;



I

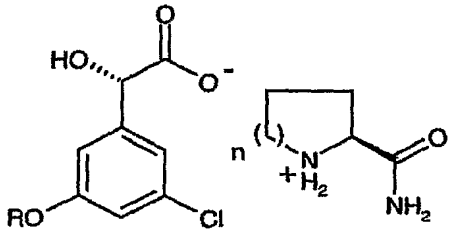
wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$;

and a chiral base (L)-cyclic amide, at an acid : base molar ratio of 1 : 0.48-0.52; and

wherein the water is in the range of 5 to 15 % (vol.) of ethyl acetate; then

(b) heating and stirring said mixture to reflux; then

(c) cooling said mixture/suspension from step (b), followed by filtering said cooled mixture/suspension to obtain a mandelic acid cyclic amide salt of formula **IV**;

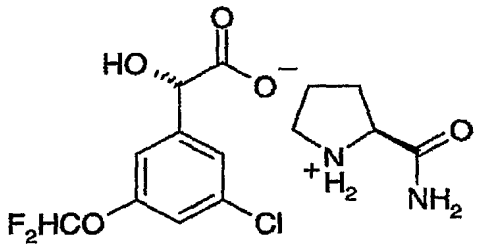


IV

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and

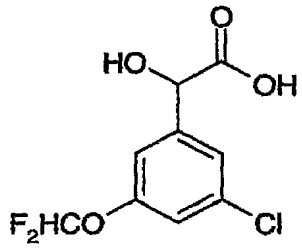
n is 0, 1 or 2.

In one embodiment of this aspect, there is provided a process, wherein R of Formula **IV** is CHF_2, and n of Formula **IV** is 1, represented by Formula **VII**;



VII

In another aspect of the invention, there is provided a process, wherein R of Formula I is CHF_2, represented by Formula V;



V

The racemic mandelic acid derivative/cyclic amide/ethyl acetate mixture in (a) of the processes may be heated to reflux, followed by addition of the water to obtain the suspension in step (b) of the processes. This suspension is normally stirred at reflux for 10 minutes before starting the cooling processes (c).

The suspension in step (c) of the processes may be cooled to 20 to 25°C for 10 to 15 hours, followed by further cooling to 15 to 19°C for additional 40 to 60 minutes. Preferably, the suspension is cooled to about 23°C for 13 hours followed by further cooling to 18°C for additional 45 minutes.

Alternatively, the suspension in (c) of the process is cooled to about 15 to 19°C for 3 to 4 hours. Preferably, the suspension is cooled to 18°C for 3 to 4 hours.

The amounts of racemic mandelic acid derivative and chiral base cyclic amide in step (a) of the processes are added at a molar ratio of 1 : 0.48-0.52 in ethyl acetate. Preferably, the molar ratio is 1 : 0.50.

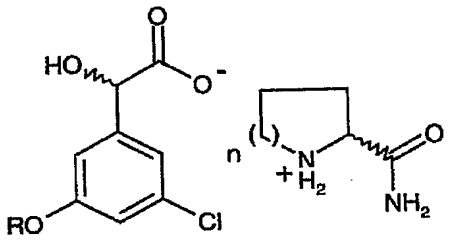
It is to be understood that the molar ratios also cover experimental variation around these limits, e.g. ± 0.005.

The added amount of water in step (a) in the processes is in the range of 5 to 15% (vol.) of ethyl acetate. This gives a solution wherein the concentration of water is 5 to 10% in ethyl acetate, e.g. 0.3 ml water added in 3.7 ml ethyl acetate is 7.5%. Preferably, the added amount of water is in the range of 5 to 10% (vol.) of ethyl acetate. Particularly preferred is when the added amount of water is in the range of 6 to 7% (vol.) of ethyl acetate.

The concentration of racemic mandelic acid derivative in the ethyl acetate and water solvent mixture is usually in the range of 0.5-2.5 mmol per ml of ethyl acetate and water. Preferably, the racemic mandelic acid derivative is added at a concentration range of 1.0-2.0 mmol per ml of ethyl acetate and water. Particularly preferred is when the racemic mandelic acid derivative is added at a concentration range of 1.0-1.2 mmol per ml of ethyl acetate and water.

The suspension comprising the salt obtained in step (c) of the processes may be further washed with ethyl acetate. The salt may be dissolved in a mixture of HCl and ethyl acetate followed by separation of the organic layer and concentrating said organic layer to dryness to obtain resolved mandelic acid derivative. Preferably, the mixture of HCl and ethyl acetate is a 1:1 (vol.) mixture of 1M HCl and ethyl acetate. The resolved mandelic acid derivative may be analysed by conventional chiral HPLC techniques.

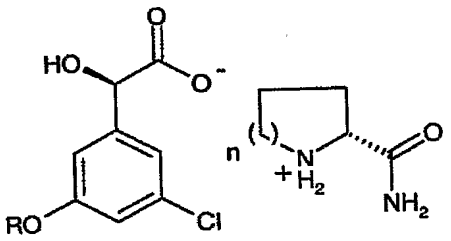
In another aspect of the invention there is provided the (*R*)/(D) or (*S*)/(L) mandelic acid cyclic amide salt having the formula **II**;



II

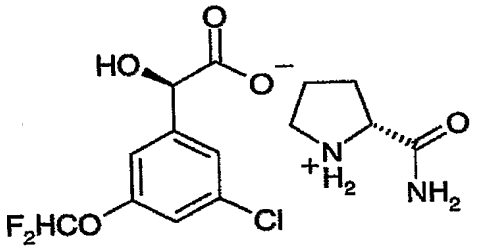
wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and n is 0, 1 or 2.

In one embodiment of this aspect there is provided a mandelic acid cyclic amide salt, represented by formula **III**;



III

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and n is 0, 1 or 2. Preferably, said mandelic acid cyclic amide salt is a mandelic acid cyclic amide salt, wherein R is CHF_2, and n is 1, represented by Formula **VI**;



VI

The said mandelic acid cyclic amide salts represented by the Formulas II, III and VI are obtainable by the processes of the present invention.

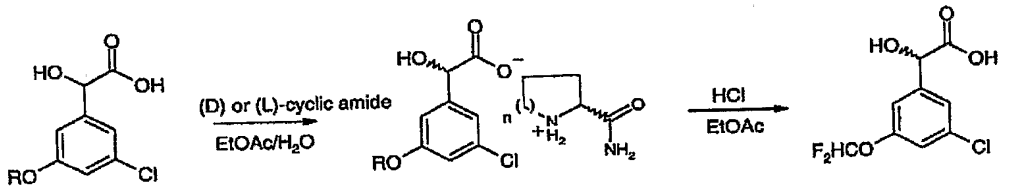
There is a need for a more convenient and more economically efficient process for the manufacturing of large scale quantities of high quality (pure) resolved mandelic acid derivatives, where factors like costs, manufacturing time, use of more environmentally friendly solvents, etcetera are vital for commercial application. The present invention provides for such a process. The processes of the invention uses an improved process for the manufacture of resolved mandelic acid derivatives in which non-expensive raw materials and thermally safe work up conditions are used to achieve these quality resolved mandelic acid derivatives ready to use in further chemical processing.

The phrase "e.e." denotes an abbreviation for enantiomeric excess and it is defined as the mole fraction denoting the enantiomers in a mixture:

% e.e. = [R] - [S]/[R] + [S]

where [R] and [S] are the concentrations of the (*R*)- and (*S*)-enantiomers. In a reaction a chiral compound is often obtained as a mixture of enantiomers. If, for example, 80% of the (*R*)-enantiomer is formed and 20% of the (*S*)-enantiomer then the e.e. is: 80-20/80+20 = 60%.

A general outline of the processes is as follows:



racemic mandelic acid derivative (*R*)- or (*S*)-mandelic acid/(D)- or (L)-cyclic amide salt resolved mandelic acid

The present invention is described in more detail in the following non-limiting examples.

Example 1-3

In these examples the following method was used: All volumes and amounts were as outlined in Table 1. The racemic mandelic acid derivative, 3-chloro,5-difluoro-methoxy mandelic acid and (D)-proline amide was added to ethyl acetate saturated in water (8.1% water in ethyl acetate) and the mixture was heated to reflux and the mixture was stirred for 10 minutes at reflux. The thin suspension was cooled to 23°C over 13 h followed by further cooling to 18°C over 40 minutes. The suspension was filtered and washed with ethyl acetate (3 x 30 ml). This gave the salt. A sample was dissolved in a 1:1 mixture of 1 M HCl and ethyl acetate. The organic layer was separated, concentrated to dryness and analysed by chiral HPLC. This showed a high degree of purity of the correct enantiomer (see Table 1) of (*R*)- 3-chloro,5-difluoro-methoxy mandelic acid.

Table 1.

Example no.	mmol MA[1]	mmol PA	Eq. PA	EtOAc (ml)	Water/EtOAc (%)	mmol MA/ ml water-EtOAc	e.e. (%)
1	1.16	0.57	0.49	0.97	8.1	1.20	84.2
2	1.16	0.57	0.49	0.51	8.1	2.27	95.3
3	1.09	0.53	0.49	0.67	8.1	1.63	90.6

MA= racemic mandelic acid derivative, 3-chloro,5-difluoro-methoxy mandelic acid.
PA= (D)-proline amide.
Eq. PA= Amount of equivalents of (D)-proline amide compared to racemic mandelic acid derivative.
EtOAc= ethyl acetate, as solution saturated in water.
Water/EtOAc (%) = concentration of water in ethyl acetate.
mmol MA/ ml water-EtOAc= concentration range of racemic mandelic acid derivative per ml of ethyl acetate and water.
e.e. (%) = enantiomeric excess defined as the % mole fraction denoting the enantiomers in a mixture.
1) Corrected for purity, i.e. initially 86% pure racemic mandelic acid derivative.

Examples 4-9

In these examples the following method was used: All volumes and amounts were as outlined in Table 2. The racemic mandelic acid derivative 3-chloro,5-difluoro-methoxy mandelic acid and (D)-proline amide were added to ethyl acetate and the mixture was heated to reflux. At reflux, water was added and the mixture was stirred for another 10 minutes at reflux. The thin suspension was allowed to cool to 18°C over 3 h (in examples

4-8; 4h in Example 9). The suspension was filtered and washed with ethyl acetate (3 x 30 ml). This gave the salt. The salt was dissolved in a 1:1 mixture of 1 M HCl and ethyl acetate. The organic layer was separated, concentrated to dryness and analysed by chiral HPLC. This showed a high degree of purity of the correct enantiomer (see Table 2) of (*R*)-3-chloro,5-difluoro-methoxy mandelic acid.

To exemplify in more detail, the following scheme was used in example 6: The racemic mandelic acid derivative 3-chloro,5-difluoro-methoxy mandelic acid (26.18 g, 93.3 mmol, 1 eq, 90% pure according to HPLC, i.e. 83.97 mmol pure racemic mandelic acid derivative) and (D)-proline amide (4.80 g, 42 mmol, 0.50 eq) was added to ethyl acetate (54.5 ml) and the mixture was heated to reflux. At reflux, 5.5 ml of water were added and the mixture was stirred for another 10 minutes at reflux. The thin suspension was allowed to cool to 18°C over 3 h. The suspension was filtered and washed with ethyl acetate (3 x 30 ml). This gave 8.6 g of the salt. A sample was dissolved in a 1:1 mixture of 1 M HCl and ethyl acetate. The organic layer was separated, concentrated to dryness and analysed by chiral HPLC. This showed 98.2% of the correct enantiomer. From the mother liquor more material crystallised which was filtered, washed and dried. This gave another 1.6 g of the salt. The free acid was analysed by HPLC and contained 99.0% of the correct enantiomer.

Table 2.

Example no.	mmol MA[1]	mmol PA	Eq. PA	EtOAc (ml)	Water (ml)	Water/ EtOAc (%)	mmol MA/ ml water-EtOAc	e.e. (%)
4	5.96	2.9	0.49	3.7	0.30	7.5	1.61	99.2
5	10.45	5.1	0.49	6.4	0.52	7.5	1.51	98.9
6	83.97	42.0	0.50	54.5	5.50	9.2	1.40	98.7
7	155.31	77.7	0.50	91.5	10.20	10.0	1.53	99.0
8	76800	38400	0.50	66800	4600	6.4	1.08	98.2
9[2]	42240	21120	0.50	33000	2500	7.0	1.19	99.6

MA = racemic mandelic acid derivative 3-chloro,5-difluoro-methoxy mandelic acid.
PA = (D)-proline amide.
Eq. PA = Amount of equivalents of proline amide compared to racemic mandelic acid derivative
EtOAc = ethyl acetate in ml.
Water/EtOAc (%) = concentration of water in ethyl acetate.

mmol MA/ ml water-EtOAc = concentration range of racemic mandelic acid derivative per ml of ethyl acetate and water.
e.e. (%) = enantiomeric excess defined as the % mole fraction denoting the enantiomers in a mixture.
1) Corrected for purity, i.e. initially 85-90% pure racemic mandelic acid derivative.
2) The suspension was allowed to cool to 18°C over 4 h.

Example 10

The racemic mandelic acid derivative 3-chloro,5-difluoro-methoxy mandelic acid (0.2 g, 0.79 mmol) and (L)-proline amide (0.05g, 0.48mmol, 0.6 eq,) was added to 1 ml dioxane and the mixture was heated to 90°C. During heat-up a thick suspension was formed. The suspension was filtered and mandelic acid liberated by extractive work up using 1 M HCl and ethyl acetate. 0.05 g enantiomer of ee: 92% was obtained.

CLAIMS

1. A process for resolving (*R*)- or (*S*)- optionally substituted mandelic acids from racemic mixturers of said optionally substituted mandelic acids by salt formation with a chiral base (D)- or (L)-cyclic amide, comprising the steps:

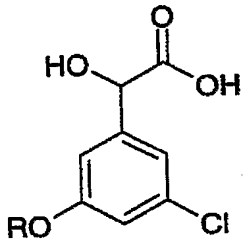
(a) forming a mixture in ethyl acetate/water of a racemic optionally substituted mandelic acid; and a chiral base (D)- or (L)-cyclic amide, wherein the base used is (D) for separation of (*R*) acids, and (L) for separation of (*S*) acids, at an acid : base molar ratio of 1 : 0.48-0.52; and wherein the water is in the range of 5 to 15 % (vol.) of ethyl acetate; then

(b) heating and stirring said mixture at reflux; then

(c) cooling said mixture/suspension from step (b), followed by filtering said cooled mixture/suspension to obtain the respective *R*/D or *S*/L mandelic acid cyclic amide salt.

2. The process according to claim 1, for resolving (*R*)- or (*S*)-mandelic acid derivatives from racemic mandelic acid derivatives by salt formation with a chiral base (D)- or (L)-cyclic amide, comprising the steps:

(a) forming a mixture in ethyl acetate/water of a racemic mandelic acid derivative of formula I;

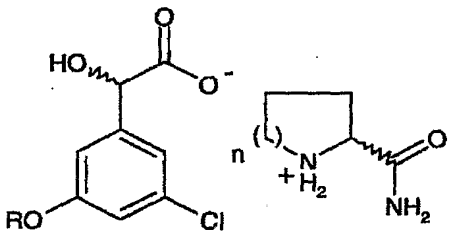


I

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and a chiral base (D)- or (L)-cyclic amide wherein the base used is (D) for separation of (*R*) acids, and (L) for separation of (*S*) acids), at an acid : base molar ratio of 1 : 0.48-0.52; and wherein the water is in the range of 5 to 15 % (vol.) of ethyl acetate; then

(b) heating and stirring said mixture at reflux; then

(c) cooling said mixture/suspension from step (b), followed by filtering said cooled mixture/suspension to obtain the respective (*R*)/(D) or (*S*)/(L) mandelic acid cyclic amide salt of formula **II**;

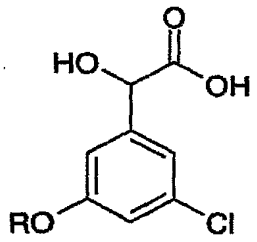


II

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and n is 0, 1 or 2.

3. The process according to claim 2, for resolving (*R*)-mandelic acid derivatives from racemic mandelic acid derivatives by salt formation with a chiral base (D)-cyclic amide, comprising the steps:

(a) forming a mixture in ethyl acetate/water of a racemic mandelic acid derivative of formula **I**;

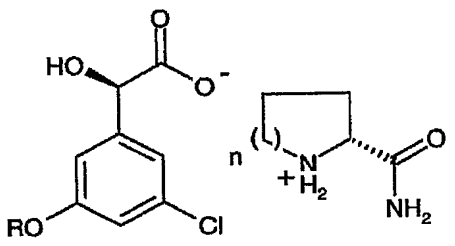


I

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and a chiral base (D)-cyclic amide, at an acid : base molar ratio of 1 : 0.48-0.52; and wherein the water is in the range of 5 to 15 % (vol.) of ethyl acetate; then

(b) heating and stirring said mixture at reflux; then

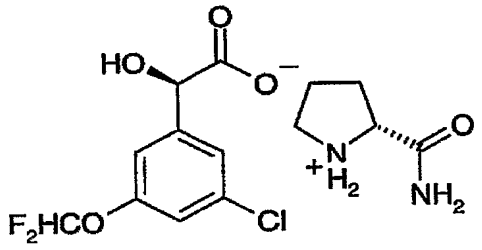
(c) cooling said mixture/suspension from step (b), followed by filtering said cooled mixture/suspension to obtain a mandelic acid cyclic amide salt of formula **III**;



III

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and n is 0, 1 or 2.

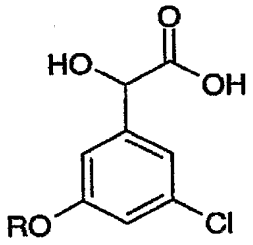
4. The process according to claim 3, wherein R of Formula **III** is CHF_2, and n of Formula **III** is 1, represented by Formula **VI**;



VI

5. The process according to claim 2, for resolving (*S*)-mandelic acid derivatives from racemic mandelic acid derivatives by salt formation with a chiral base (L)-cyclic amide, comprising the steps:

(a) forming a mixture in ethyl acetate/water of a racemic mandelic acid derivative of formula **I**;



I

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$;

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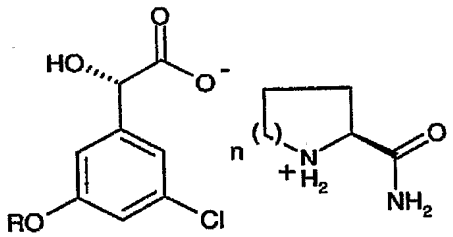
and a chiral base (L)-cyclic amide, at an acid : base molar ratio of 1 : 0.48-0.52; and wherein the water is in the range of 5 to 15 % (vol.) of ethyl acetate; then

(b) heating and stirring said mixture to reflux; then

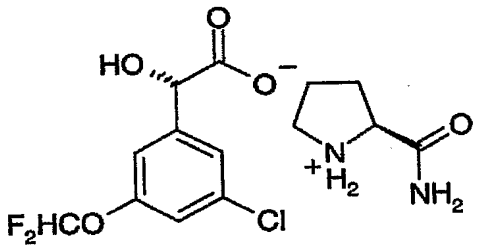
(c) cooling said mixture/suspension from step (b), followed by filtering said cooled mixture/suspension to obtain a mandelic acid cyclic amide salt of formula **IV**;



IV

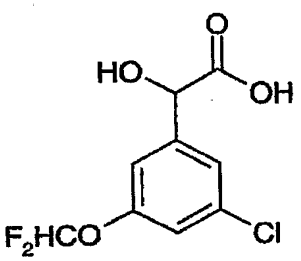
wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and n is 0, 1 or 2.

6. The process according to claim 5, wherein R of Formula **IV** is CHF_2, and n of Formula **IV** is 1, represented by Formula **VII**;



VII

7. The process according to any one of claims 2 to 6, wherein R of Formula **I** is CHF_2, represented by Formula **V**;



V

8. The process according to any one of claims 1 to 7, wherein the suspension in step (c) in any of said claims is cooled to 20 to 25°C for 10 to 15 hours, followed by further cooling to 15 to 19°C for additional 40 to 60 minutes.

9. The process according to claim 8 wherein said suspension is cooled to 23°C for 13 hours followed by further cooling to 18°C for additional 45 minutes.

10. The process according to any one of claims 1 to 7, wherein the suspension in step (c) in any of said claims is cooled to 15 to 19°C for 3 to 4 hours.

11. The process according to claim 10, wherein the said suspension is cooled to 18°C for 3 to 4 hours.

12. The process according to any one of claims 1 to 11, wherein the racemic mandelic acid derivative and chiral base cyclic amide are added such that said acid and said base forms a mixture at an acid : base molar ratio of 1 : 0.50.

13. The process according to any one of claims 1 to 12, wherein the added amount of water in step (a) in any of said claims is added in the range of 5 to 10% (vol.) of ethyl acetate.

14. The process according to claim 13, wherein said added amount of water is added in the range of 6 to 7% (vol.) of ethyl acetate.

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15. The process according to any one of claims 1 to 14, wherein said racemic mandelic acid derivative is added at a concentration range of 0.5-2.5 mmol per ml of ethyl acetate and water.

16. The process according to claim 15, wherein said racemic mandelic acid derivative is added at a concentration range of 1.0-2.0 mmol per ml of ethyl acetate and water.

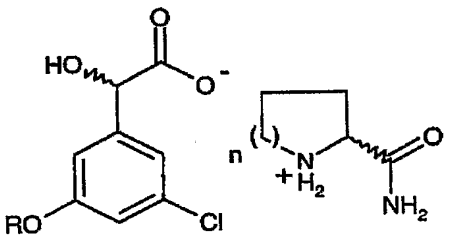
17. The process according to claim 16, wherein said racemic mandelic acid derivative is added at a concentration range of 1.0-1.2 mmol per ml of ethyl acetate and water.

18. The process according to any one of claims 1 to 17, wherein the salt obtained in step (c) in any of claims 1 to 17, is further washed with ethyl acetate.

19. The process according to any one of claims 1 to 18, wherein the salt obtained in step (c) in any one of claims 1 to 18, is dissolved in a mixture of HCl and ethyl acetate followed by separation of the organic layer and concentrating said organic layer to dryness to obtain resolved mandelic acid derivative.

20. The process according to claim 19, wherein the mixture of HCl and ethyl acetate is a 1:1 (vol.) mixture of 1M HCl and ethyl acetate.

21. An (*R*)/(D) or (*S*)/(L) mandelic acid cyclic amide salt having the formula **II**;



II

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and n is 0, 1 or 2.

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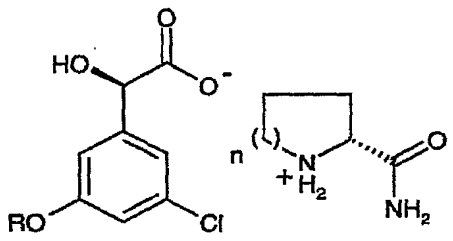
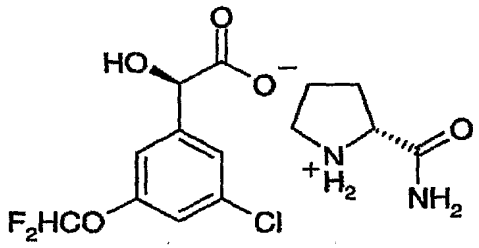
22. The mandelic acid cyclic amide salt according to claim 21, represented by formula **III**;



III

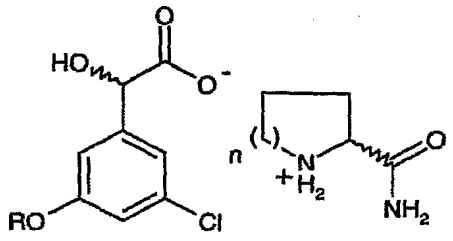
wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and n is 0, 1 or 2.

23. The mandelic acid cyclic amide salt according to claim 22, wherein R is CHF_2, and n is 1, represented by Formula **VI**;



VI

24. An (*R*)/(D) or (*S*)/(L) mandelic acid cyclic amide salt having the formula **II**;



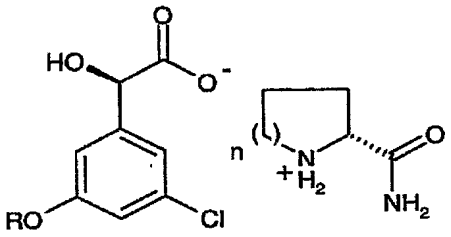
II

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and

n is 0, 1 or 2;

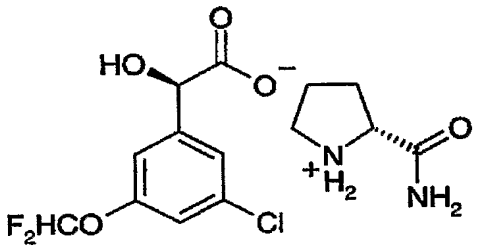
obtainable by a process acoording to any one of claims 1 to 19.

25. The mandelic acid cyclic amide salt according to claim 24, represented by formula **III**;



III

26. The mandelic acid cyclic amide salt of claim 24, wherein R is CHF_2, and n is 1, represented by formula **VI**;



VI

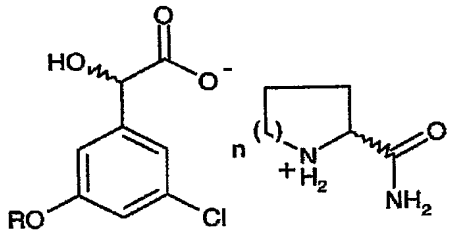
27. The use of a mandelic acid cyclic amide salt according to any one of claims 21 to 23 in manufacture of pharmaceutical products.

28. The use of a mandelic acid cyclic amide salt according to any one of claims 21 to 23 as chemical intermediates.

29. The use of a mandelic acid cyclic amide salt according to any one of claims 21 to 23 as chemical intermediates in manufacture of pharmaceutical products.

ABSTRACT

The present invention relates to a new process for the resolution of mandelic acid derivatives from racemic mandelic acid derivative mixtures by salt formation with chiral base cyclic amides. The invention also relates to the mandelic acid cyclic amide salts as well as to the use of the resolved mandelic acid derivatives as intermediates suitable for large-scale manufacturing of, for example, pharmaceutical compounds. The mandelic acid cyclic amide salts may be illustrated by the Formula **II**;



II

wherein R is selected from CHF_2, H, C_{1-6} Alkyl, CH_2F, $CHCl_2$ and $CClF_2$; and

n is 0, 1 or 2.